Peer Review File

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Reviewer A

General Comments:

Comment 1: It would be helpful to have further specifics on the type of review that was performed for this article. Is this a systematic review, narrative review, scoping review, rapid review, historical review, a state of the art review? What methodological framework was used when designing the study? (see PMID: 19490148). A "comprehensive" review (Line 153) is not widely accepted as type of formal review. If a methodological framework is retrospectively adopted, would use this as an opportunity to discover literature/references that might have been missed or overlooked in the writing of the first draft of the manuscript.

Reply 1: this was a narrative in its framework. The review did not have a specified, methodical criteria for inclusion of studies beyond subjective author evaluation of relevance, quality, and significance of included publications to the review topic which is in accordance with examples of narrative review checklists noted on the Ann Transl Med. The references used were agreed upon after independent review of references by the other authors.

Changes in the text: replaced "comprehensive" with narrative and scoping, added that significance was an additional selection factor in discussed publications in this review.

Comment 2: Which databases/resources were searched to provide the included references?

Reply 2: Chosen references were sourced and searched from Pubmed, Google Scholar, Library of Congress, and Cochrane Review.

Changes in the text: wrote in description of the review where the sources were taken from, as described above.

Comment 3: Overall, the organizational structure is well done. Can the authors comment about the availability of data regarding documented/captured CC scores reported for the publications mentioned in the section HIPEC Outcomes and how CC score influenced the measured outcomes?

(either in the Outcomes section itself, the Completeness of Cytoreduction section, or both?)

Reply 3: Both Ji et al and Glehen et al. directly state their studies' CC scores. Some meta-analyses cited save the CC scores as supplementary data or only present the synthesized data combined from various utilized studies in their analyses.

Changes in the text: clarified that the paragraph's conclusions regarding impact of CC on HIPEC outcomes are based on highly specified data from study populations over 100 (relatively large sample size for this treatment in this cancer type)

Comment 4: Needs the addition of a Limitations sections that offers a high-level overview/summary of the biggest limitations to the current literature for this field of study.

Reply 4: A limitations paragraph was included to discuss the drawbacks of our review in terms of understanding its utility in analyzing the current literature for HIPEC for gastric cancer.

Changes in the text: Limitations paragraph created before the conclusion.

Comment 5: As currently written, this article is at extremely high risk of bias secondary to a non-systematic method of literature review.

Reply 5: It is true that this review likely has high risk of bias given the subjective method of selecting references in the literature for discussion. However, the intent of this review was to provide an overview of the use of HIPEC in gastric cancer, painted in relatively broad strokes without specified guidelines or topics to discuss given. As HIPEC in gastric cancer is still a relatively rare treatment metholodolgy not widely and routinely practiced, there are a paucity of data regarding various factors that may influence HIPEC, and even more so limited studies that fall into clinical or non-clinical trials of significant power. Moreover, reporting by each study is not standardized—many studies report a variety of outcomes. Reviews that summarize these outcomes become meta-analyses, which are also studied and critiqued here in this narrative review. By intents and purposes, choosing a more systematic approach and hence turning this review into a systematic review/meta-analysis would not be necessarily more novel than the literature cited within this review itself, and would thereby lose its utility, as there would be insufficient data and scope to touch upon more basic science/translational or upcoming outcomes reported in various other studies noted in this review.

Changes to the text: Acknowledged that indeed this study is inherently at risk for bias given

subjective and non-systematic/methodological framed selection of presented studies and data.

Specific Comments:

Comment: Line 51: Recommended by who? A citation would be helpful here.

Reply: NCCN Clinical Practice Guidelines in Oncology: gastric cancer version 4. Plymouth Meeting (PA): National Comprehensive Cancer Network; 2020. Available: https://www.nccn.org/professionals/ physician_gls/pdf/gastric_blocks.pdf [login required] (accessed 2020 Mar. 10).

Changes in the text: Specifically identified the full length name of the NCCN guideline version supporting this statement beyond the original text of just "NCCN".

Comment: Line 60: Are these findings from a human or non-human animal model?

Reply: Human samples from cancer patients, not a xenograft of non-human animal model

Changes in text: specified that the samples were taken from human patients

Comment: Lines 54: Are these studies widely available/performed clinically?

Reply: Not clinically translatable at the moment. However, these studies are available in peer-reviewed, public academic journals and have been published by both Western and Eastern institutions. A variety of these studies have been published, but thus far no significant clinical trials have started from GCPC cell analyses as of yet, although retrospective studies from clinical samples have increased, such as below (not cited in this study for brevity and thematic clarity).

Jiang RP, Xiong XJ, Qiu XS, Wang EH, Wu GP. The Morphological Analysis of Cells in the Peritoneal Washing Fluids of Patients with Gastric Cancer. Cell Transplant. 2019 Nov;28(11):1384-1389. doi: 10.1177/0963689719864318. Epub 2019 Aug 1. PMID: 31366210; PMCID: PMC6802142

Pan G, Ma Y, Suo J, Li W, Zhang Y, Qin S, Jiao Y, Zhang S, Li S, Kong Y, Du Y, Gao S, Wang D. Discovering Biomarkers in Peritoneal Metastasis of Gastric Cancer by Metabolomics. Onco Targets Ther. 2020 Jul 27;13:7199-7211. doi: 10.2147/OTT.S245663. PMID: 32801750; PMCID: PMC7394602.

Changes in text: No additions to the text, as there are no clinically translatable studies. For the

intent of this paragraph, it is to mention that the possibility of utilization of cytologic washings/ascites in GCPC to predict HIPEC outcomes overall is promising, transitioning into the following paragraphs detailing said studies utilizing washings/ascites.

Comment: Line 55-59: Does the molecular classification proposed in 2014 by the Cancer Genome Atlas (TCGA) project have clinical significance? (PMID: 25079317)

Reply:

EBV, CIN, MSI, and GS tumors = 4 categories of gastric cancer they proposed. Based on search of current literature, there are no major clinical studies that detail HIPEC response based on those specific subtypes. There are other studies (not cited here, again due to the focus of the paragraph for studies discussing specifically genetic/molecular subtypes impacting HIPEC) that describe progression of GC but not in context of HIPEC.

Specifically, within these subtypes, the Asian Cancer Research Group splits GC into MSI and MSS, with MSS GC types being divided into the later mentioned EMT or non-EMT types

Certainly the subtypes matter overall for GC prognosis/outcomes (MSI with better overall outcomes, mostly intestinal, distal tumors with less nodal metastases risk, etc) as discussed in this recent review (PMID 29796937). However, only EMT is discussed predominantly in this study and other molecular subtype studies in context of peritoneal spread that can be targeted by HIPEC, hence the general omission of discussion of the TCGA studies in this review since our review discusses HIPEC for GC rather than all GC outcomes/ treatment factors

Changes in text: Added several sentences to clarify how EMT fits into molecular subtypes and its relation to diffuse vs intestinal gastric cancer. No additional molecular classification-related statements were made as there are no relevant studies / evidence in the literature on our search that specifically discuss them in relation to HIPEC outcomes for gastric cancer.

Comment: Line 56: How does this classification correspond to diffuse-type gastric cancer (DGC) and intestinal-type gastric cancer (IGC) and underlying mutations? (PMID: 33724653, PMID: 24816253)

Reply: Epithelial-mesenchymal transition is found in both diffuse and intestinal GC. However, the exact genes dictating the EMT process differ between the two GC types and are not yet fully known

as it appears there are numerous genes that may be involved in this pathway. Thus, based on this, we framed our discussion on EMT and non-EMT types since that was more relevant to PC development (PMID 33353109)

Changes in text: added a reference, added that EMT is present in both diffuse and intestinal gastric cancer and that the underlying mutations are not yet well defined/ongoing body of study.

Comment: Line 74: This is the first use of the acronym PCI- please define.

Reply: Did not notice on our initial draft—thank you for the reminder. Will change.

Changes in text: defined the acronym of PCI to be peritoneal carcinomatosis index

Comment: Line 81: "the median survival of GC patients with positive cytology is similar to GCPC patients despite curative resection"- This language/meaning is unclear.

Reply: the intent was to discuss how patients who underwent total CRS with macroscopic metastases had similar median survival to patients who just had positive cytology, suggestive that positive cytology likewise has a similar prognosis/overall end outcome to macroscopic disease

Changes in text: Reworded sentence in mention for clarity

Comment: Line 84: Please clarify the term "prophylactic HIPEC" (see PMID: 31618869); I don't understand the logic that connects the patient population who converts from positive to negative cytology from those that underwent prophylactic HIPEC. HIPEC would not be classified as prophylactic for patients who ever had positive cytology. This claim/statement is misleading.

Reply: We agree with the point that the original phrased claim is misleading. Our intent was to describe how HIPEC could prevent transition to macroscopic disease and was preventative in that measure.

Changes in text: Reworded to properly classify prophylactic HIPEC as HIPEC for those without positive cytology or macroscopic disease

Comment: Line 85: This section seems as if it fits better in the first category Histologic Subtypes

Reply: we understand the rationale behind the fit in terms of flow of the manuscript organization / topics.

Changes in text: Moved paragraph to be more cohesive with the discussion of molecular subtypes transitioning now to histologic subtypes

Comment: Line 93: Decreased survival following HIPEC?

Reply: the intent was to discuss that patients who had high burden of pre-operative systemic chemotherapy did worse despite receiving HIPEC, demonstrating prolonged duration of preoperative chemotherapy reduced patient survival in patients suitable for CRS and HIPEC

Changes in text: Added “eligible for CRS and HIPEC” and "despite receiving HIPEC" to further specify the context of this outcome

Comment: Line 100: Would title this section Intraperitoneal Chemotherapy Regimens

Reply/Changes in text: Retitled to say “Intraperitoneal chemotherapy regimens”

Comment Line 115: Use of the word “surgery” here (and throughout) is extremely vague and is impossible to interpret.

Reply: Specified to say curative-intent resection +/- cytoreduction-- many meta analyses include Eastern and Western cohort patients of various gastric cancer types/locations of various stages, and thus it is hard to generalize specifically that they get "radical gastrectomy" etc, as the actual procedure range is wide but the analysis is based on some form of curative intent surgical resection with HIPEC

Other reviews (e.g. PMID 31618869, 35481913) similarly generalize wording as HIPEC with surgery vs surgery alone given heterogeneity of limited studies available for HIPEC and GC causing a wide range of what each study would define as the surgical procedure involved in treatment cohorts

Changes in text: changed wording of surgery to be curative-intent resection with/without cytoreduction, as there is no ability to be more specific as the studies referenced themselves don’t even define what “surgery” is.

Comment: Line 127: This statement is unclear: “no PC or negative peritoneal cytology after final HIPEC”

Reply: Rephrased to hopefully more clearly convey there was no peritoneal disease at all following HIPEC

Changes in text: Changed to say “no macroscopic PC with negative peritoneal cytology after HIPEC”

Comment: Line 144-145: As referenced above, prophylactic HIPEC is HIPEC done for patients without clinically evident metastases or negative peritoneal cytology. The paper referenced by Sun et al was not a study of prophylactic HIPEC. From the Desidero study, patients with peritoneal deposits at the time of HIPEC would not be included in the patient population undergoing prophylactic HIPEC. This section requires revision.

Reply: this study by Desidero et al included patients who did not have peritoneal disease and demonstrated that they had lower peritoneal lesion occurrence/metastasis and disease recurrence, and thus we included this study as a prophylactic study since technically part of the cohort was PC and cytology negative prior to HIPEC and therefore outcomes were relevant in a prophylactic view. We understand that part of the population reported in the Desidero study did have peritoneal deposits, but their reported analyses do parse the differences between groups which did have peritoneal deposits at time of HIPEC (not prophylactic) and those who did NOT have peritoneal disease who underwent HIPEC (thereby prophylactic).

In regards to the study by Sun et al, it was a meta-analysis as well, and as the commentor correctly states, the intent was not to study prophylactic HIPEC itself. However, their study population did include patients who met criteria for having received prophylactic HIPEC.

Per their methods:

“Inclusion criteria included all articles concerning patients with gastric cancer who were allocated randomly to receive surgery associated with intraperitoneal hyperthermic chemotherapy versus surgery without intraperitoneal hyperthermic chemotherapy. The advanced gastric cancer of the patients consisted of macroscopic serosal invasion without distant metastases or peritoneal carcinomatosis”.

While Sun et al do not explicitly mention “prophylaxis”, they devote several portions of their discussion to the findings that their meta-analyses produced demonstrating prevention of local

peritoneal recurrence in their described study population that did NOT have distant metastases or peritoneal disease, and therefore do describe a possible prophylactic HIPEC population.

Changes in text: none

Comments: Line 149: Is it true that these studies suggest that HIPEC prevents peritoneal metastasis in GC?

Reply: It is unclear if it can, but the data suggests that there are some patients without PC who underwent HIPC who were less likely to develop PC despite initial stage and such compared to non-HIPEC patients. The data thus far is inconclusive given study heterogeneity (as similarly stated in another review, PMID 31618869). There are still clinical trials being run to determine if prophylactic HIPEC truly can prevent PC, as there are minimal RCTs discussing this

Changes in text: None—the purpose of the discussion of the trials is actually to even discuss whether these findings are true/the implications of data of discussed studies. Within the studies used in this review, several of the references themselves explicitly state that their findings suggest prevention of peritoneal metastasis.

Comments: Line 160-161: Unclear what the joint group includes/means. What does “surgery” mean in this context? Line 161/163: What does “surgery only” mean here- complete cytoreduction? Was the % CC-0 reported in these patient cohorts?

Reply: Similar to comments earlier, each study varies in each surgical approach/procedure, and thus for simplicity, in our review, "surgery" is used for brevity in place of specifically listing each study's surgical procedure both for general clarity/overview and in order to meet the word limits placed on the review as well as to address the variety and/or even the lack thereof of surgical procedure description for each study cited. In this instance, this study by Cui et al had the manuscript itself refer to these groups as "surgery, neoadjuvant, and joint". They did not specify the exact surgical procedures and stated the surgery group as "surgical treatment". They did not specify %CC-0 or if cytoreduction was performed, unlike other studies which did report proportions/made their cytoreduction data available.

Joint group, in this study, was defined as patients who received neoadjuvant plus "surgical

treatment" plus HIPEC

Changes in text: defined what the “joint” group was (neoadjuvant plus surgery plus HIPEC)

Comment: Line 256: Missing a “.”

Reply/Changes in text: Added the period

Comment: Line 268: Which malignancies? Can you cite?

Reply: Can provide citations for common malignancies with peritoneal metastases

Changes in text: added citation (51). Explicitly named malignancies: peritoneal mesothelioma, colorectal cancer, and appendiceal

Comment: Line 279: Can you offer a citation for the Chicago Consensus guidelines?

Reply/Changes in text: Added reference 52 for citing Chicago Consensus guidelines.

Reviewer B

This review encompasses in brief detail the hot topics in the treatment of peritoneal carcinomatosis from gastric cancer.

Given the scope of the journal and the completeness of the review, I have no comments to do and I commend the authors for their important effort in understanding the value of CRS plus HIPEC for the treatment of gastric cancer with peritoneal carcinomatosis or positive peritoneal cytology.